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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
| 10/642,974 | 08/18/2003 | Martin Michaelis | DEAV20020064US NP | 3394 |

5487 7590 03/29/2006

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EXAMINER

KWON, BRIAN YONG S

ART UNIT

PAPER NUMBER

1614

DATE MAILED: 03/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/642,974

Applicant(s)

MICHAELIS ET AL.

Examiner

Brian S. Kwon

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 January 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 2-14, 16 and 17 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 2-14, 16 and 17 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date <u>9/23/04</u> . | 6) <input type="checkbox"/> Other: _____ |

bDETAILED ACTION

Applicants Response to Restriction Requirement Acknowledged

1. Applicant's election, with traverse, with the Group I invention (claims 1 to 11 and 13 to 14) along with N-[(S)-2-dipheylamino-2-(5-oxo-4,5-dihydro[1,3,4]oxadiazol-2-yl)ethyl]-2-(2-methylaminopyrimidin-4-yl)-1H-indole-5-carboxamide, is acknowledged.

Applicants traverse the restriction requirement on the grounds that there would be no burden in searching the entire groups. This argument is not persuasive, as claimed invention would be distinctive, each from the other for the reason of the record. Furthermore, the search of the entire groups in the non-patent literature (a significant part of a thorough examination) would be burdensome. Therefore, the requirement is still deemed proper, and made Final.

2. Acknowledgment is made of applicant's canceling of claims 1 and 15 and amending claims 2, 4, 12, 13, 14, 16 and 17 by the amendment filed January 11, 2006. The claims 12 and 17 are amended such that old claims 12 and 17 are no longer drawn to a process of making the pharmaceutical product. Accordingly, claims 12 and 17 will be included in the Group I invention. Claims 2-14 and 16-17 are currently pending for prosecution on the merits.

Priority

3. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Germany 10237723.5 filed 08/17/2002.

Information Disclosure Statement

4. Acknowledgement is made of applicant's submitting of the information disclosure statement (IDS) on 09/23/04. The submission is in compliance with the provisions of 37

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CFR 1.97. Accordingly, the information disclosure statement (IDS) has been considered by the examiner.

5. With respect to applicant's reference to "10/642,970", "60/570,146" and "10/842,427", it is not proper to list the copending application information in Patent Documents section.

Accordingly, it will be listed in non-patent literature documents in PTO 892.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 2-7, 12-14 and 16-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating pain associated with arthritis with N-[(S)-2-dipheylamino-2-(5-oxo-4,5-dihydro[1,3,4]oxadiazol-2-yl)ethyl]-2-(2-methylaminopyrimidin-4-yl)-1H-indole-5-carboxamide, does not reasonably provide enablement for treating pain with compounds represented by the formula I or Ia. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the

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presence or absence of working examples; and (8) the quantity of experimentation necessary.

When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The invention relates to a method of treatment of pain with I κ B-kinase inhibitor compounds represented by the formula I or Ia.

The instantly claimed I κ B-kinase inhibitors represented by the formula I or Ia are generally recognized in the art as being distinct from each other because of their diverse chemical structures depending upon different substituents. For instance, the instant compounds include compounds classified in 514, subclass 393-396, 415-419 and various subclass of classes 540, 544, 546, 548 and 549.

There are no known compounds of similar structure which have been demonstrated to treat all types of pain. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of pharmacology.

The relative skill of those in the pharmaceutical arts or unpredictability of the pharmaceutical art is very high. Applicant has not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the compounds encompassed by the instant claims. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970).

The claims are very broad due to the vast number of possible compounds represented by the formula I or Ia that are described as being an I κ B-kinase inhibitor. Structures of compounds vastly differ from each other by different substituents E, R1, R2, R3, R4, R5, R6 and etc...

Furthermore, the breadth of the claims is further exacerbated by the instantly claimed wide range of pain treatment including musculoskeletal disease, menstruation pain, arthritic pain, pain associated with intestinal inflammation, pain associated with cardiac muscle inflammation, pain associated with multiple sclerosis, neuritic pain, neuropathic pain, pain associated with carcinoma and sarcoma, pain associated with AIDs, pain associated with chemotherapy, amputation pain, headache, trigeminal neuralgia, post-operative pain, pain associated with gout, pain following jaw-bone surgical intervention and etc...

The instant specification discloses pain assay (pages 33-40) to test the compound represented by the formulas in vivo and discloses that the compound of 13 (N-[(S)-2-diphenylamino-2-(5-oxo-4,5-dihydro[1,3,4]oxadiazol-2-yl)ethyl]-2-(2-methylaminopyrimidin-4-yl)-1H-indole-5-carboxamide) is effective in reducing pain associated with joint or knee inflammation. However, there is no demonstrated correlation that the tests and results apply to all of the compounds or disease conditions associated with pain embraced by the instant claims.

As discussed above, it is not known yet that a single agent is effective against all types of pain. For instance, neuropathic pain differs from acute nociceptive pain, which is caused by the normal activation of neural pathways in response to pain-initiating stimulus, and acquires different types of treatment as to the acute nociceptive pain (See "Neuropathic Pain: Diagnosis, Treatment, and the Pharmacist's Role in Patient Care, Pharmacy Times, 2005). Therefore, the

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skilled artisan would turn to undue amount of trial and error to find out which disease or condition would be response to the administration of said I κ B-kinase inhibitors.

In addition, the specification does not provide sufficient guidance in how to use vast number of possible compounds represented by the formulas, other than compound of 13. The specification provides no guidance, in the way of enablement for the full scope of all compounds that are potentially suitable for the invention work similarly as to the compound 13. The skill artisan would have not known that which compounds are capable of accomplishing the desired result of the claimed invention without undue amount of experimentation. The instantly claimed invention necessitates an exhaustive search for the embodiments suitable to practice the claimed invention.

As discussed above, although the specification describes the activity of the compound 13 as the sole working example, there is insufficient guidance in the specification that any compounds represented by the formulas that may not necessarily have close structural similarity would have similar properties as the compound 13. In view of limited numbers of working examples, the insufficient amount of guidance present in the specification, the nature of the invention, the state of art, the breadth of the claim and the relative skills of the artisan and the predictability of the pharmaceutical art where many specific differences or different physicochemical properties are existed among unrelated structural compounds would take “undue painstaking experimentation” to practice the invention commensurate in scope with these claims.

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Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

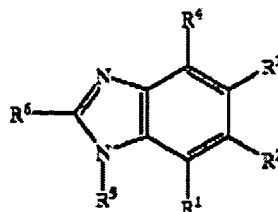
The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 2-14 and 16-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ritzeler et al. (US 6358978 B1).

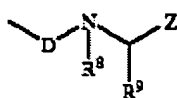
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Ritzeler discloses the compounds of formula I

having

IkB kinase inhibitor activity wherein R1, R2, R3 and R4 is radical of formula II



for the treatment of rheumatoid arthritis and osteoarthritis

(conditions characterized by inflammation of join, usually accompanied by pain, swelling and stiffness).

The claims differ from the reference by reciting a specific species and a more limited genus than the reference. However, it would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the genus taught by the reference, including those of the claims, because an ordinary artisan would have the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as the genus as a whole, in absence evidence to the contrary.

Conclusion

8. No Claim is allowed.
9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached on (571) 272-0951. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Brian Kwon
Patent Examiner
AU 1614

A handwritten signature in black ink, appearing to be 'Brian Kwon', with a long horizontal stroke extending to the right.